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Cost-Effectiveness of Nucleoside Reverse Transcriptase Inhibitor Pairs in Efavirenz-Based Regimens for Treatment-Naïve Adults with HIV Infection in the United States

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ABSTRACT

Objective: To estimate the cost-effectiveness of once-daily tenofovir/emtricitabine compared with twice-daily zidovudine/lamivudine and once-daily abacavir/lamivudine in treatment-naïve adults with HIV-1 infection in the United States. **Methods:** A Markov model with four therapy lines and six health states based on CD4$^+$ cell-count ranges was developed to estimate lifetime costs and health outcomes. Efficacy data (virologic response and CD4$^+$ cell-count changes) for first-line therapy were from 144-week results of Study 934 comparing tenofovir/emtricitabine with zidovudine/lamivudine and 48-week results of Study CNA30024 comparing abacavir/lamivudine with zidovudine/lamivudine, all in combination with efavirenz. Data from Study CNA30024 for abacavir/lamivudine were adjusted to allow for an indirect comparison with tenofovir/emtricitabine. Subsequent therapy lines were based on likely baskets of antiretroviral therapy recommended by US treatment guidelines. Utility values, mortality rates, and costs (2009 US dollars) were obtained from published sources. Base-case results were tested in sensitivity and variability analyses. **Results:** Average discounted results showed that individuals using tenofovir/emtricitabine were predicted to remain on first-line therapy for 7.7 years, accrue lifetime costs of $747,327, and experience 15.75 quality-adjusted life-years (QALYs), compared with 6.0 years, $777,090, and 15.68 QALYs for individuals using abacavir/lamivudine and 5.8 years, $778,287, and 15.44 QALYs for individuals using zidovudine/lamivudine. Tenofovir/emtricitabine was cost-effective compared with the other two first-line regimens in more than 75% of all probabilistic sensitivity analysis simulation runs for every willingness-to-pay threshold between $0 and $250,000 per QALY gained. Results were robust in variability and one-way sensitivity analyses. **Conclusions:** Tenofovir/emtricitabine was predicted to be more effective and cost-saving compared with abacavir/lamivudine and zidovudine/lamivudine in treatment-naïve adults with HIV-1 infection in the United States.

Keywords: AIDS, cost-effectiveness analysis, drug combinations, Markov model.

Introduction

Major therapeutic advances in the 15 years since the introduction of highly active antiretroviral therapy (HAART) have led to a reduction in morbidity and mortality specifically due to acquired immune deficiency syndrome (AIDS) [1–5] and an increase in life expectancy (37.3 years postinfection) for individuals with human immunodeficiency virus (HIV) infection [6]. Rising antiretroviral drug costs and longer life expectancies have led to higher lifetime treatment costs, increasing from $94,000 in 1992 [7] to over $600,000 in 2004 [8]. Therefore, costs of antiretroviral regimens have become important considerations in addition to efficacy and safety.

First-line therapy plays a significant role in each individual's long-term health outcomes and total health care costs. Durable suppression of plasma HIV ribonucleic acid (RNA) inhibits disease progression and reduces disease-related morbidity and mortality [9]. First-line therapy currently represents each individual's best chance at durable viral suppression because resistance is low and adherence to relatively tolerable and simple regimens (i.e., regimens with low pill burden and daily dosing) is likely to be high [10–12]. The choice of initial therapy is important because short-term outcomes (i.e., viral suppression, side effects, and development of resistance) may affect an individual's duration on first-line therapy [13] and thus progression through subsequent lines of therapy. Delaying more complex and expensive therapy regimens represents an additional benefit potentially conferred by longer first-line treatment durations.

For treatment-naïve individuals with HIV-1 infection, United States (US) treatment guidelines recommend using the nucleotide/nucleoside reverse transcriptase inhibitor (NRTI) fixed-dose combination tenofovir DF/emtricitabine (TDF/FTC) with the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV), one of two protease inhibitors (PI) boosted with low-dose ritonavir (/r), or the integrase strand transfer inhibitor raltegravir [9]. The fixed-dose combinations abacavir/lamivudine (ABC/3TC) and zidovudine/lamivudine (ZDV/3TC) are listed as alternative NRTI pairs.

Studies testing EFV-based regimens in treatment-naïve individuals have shown that more individuals receiving TDF/FTC ex-

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perienced virologic response than individuals receiving other NRTI pairs [14], including ZDV/3TC [15–17] and ABC/3TC [18–21]. Additionally, a recent meta-analysis found that TDF/FTC was more effective than ABC/3TC when used with a boosted PI as a first-line regimen [22]. For treatment-naïve individuals overall, NNRTI-based regimens have been associated with better efficacy [13,23–26] and longer average treatment duration [13,27] than PI-based regimens.

This study evaluates the cost-effectiveness of once-daily TDF/FTC compared with twice-daily ZDV/3TC and once-daily ABC/3TC, each used in combination with EFV in treatment-naïve adults with HIV-1 infection in the US, to highlight the potential effects of the choice of first-line NRTI pair on long-term costs and health outcomes.

Methods

Model overview

A Markov model with a 1-year cycle period was developed in Microsoft Excel (Microsoft Corporation, Redmond, WA) to follow a population of treatment-naïve HIV-positive individuals as they progressed through first-line, second-line, third-line, and non-suppressive therapy (Fig. 1). Costs and health outcomes were calculated for each of three first-line HAART regimens being compared: TDF/FTC, ABC/3TC, and ZDV/3TC, each used in combination with EFV (referred to hereafter by NRTI pair).

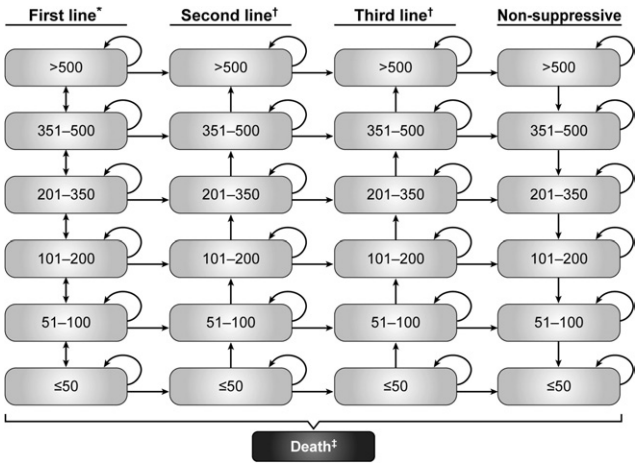

Fig. 1 – Markov model with health states based on CD4⁺ cell count. *Individuals on first-line therapy can transition to any CD4⁺ cell-count health state (not just the adjacent health states) in a given year and are at risk for adverse events including anemia, lipodystrophy, and myocardial infarction. Individuals in the ABC/3TC arm incur one-time costs for HLA-B*5701 screening, and individuals in the TDF/FTC arm incur annual costs for renal monitoring. †Individuals on second- and third-line therapies can remain in their current health state or transition upward in a given year. The model makes this assumption because estimates of person-level variation around mean CD4⁺ cell-count increases were not available from published sources and because, in clinical practice, individuals would typically switch to a new therapy regimen upon virologic failure (i.e., before CD4⁺ cell-count decline begins). ‡Individuals may transition to death from any health state. For deaths related to AIDS, transition probabilities vary by CD4⁺ cell count; for deaths unrelated to AIDS, transition probabilities vary by age and gender and increase over time to reflect aging of the cohort. 3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; TDF, tenofovir DF. Arrows indicate annual transitions.

Using clinical trial data at various time points, the model tracked the percentage of individuals in each arm who remained on first-line therapy and who had HIV-1 RNA less than 400 copies/mL. Those individuals who dropped out of this group for any reason, including adverse events, lack of initial virologic response, or loss of initial virologic response, switched from first-line to second-line therapy. A threshold viral load of 400 copies/mL was chosen as a clinically relevant point above which individuals would likely switch to a new regimen.

Individuals entered the model in one of six possible Markov-model health states defined by CD4⁺ cell-count ranges (> 500, 351–500, 201–350, 101–200, 51–100, and 0–50 cells/μL). Every year, individuals remained in their current health state or moved to another state of the model, where transition probabilities were estimated from clinical trial and observational cohort data. There was a chance of death from any therapy line, HIV-1 RNA level, or CD4⁺ cell-count range.

The model was developed to focus on different first-line regimens from the NRTI drug class when combined with EFV. First-line therapies were modeled using clinical trial data. As individuals switched to later lines of therapy, costs and efficacy were based on a basket of regimens recommended by the US treatment guidelines [9].

The analysis took a US societal perspective. Incremental cost-effectiveness ratios included direct medical costs in the numerator and either life-years or quality-adjusted life years (QALYs) in the denominator. As recommended for health economic analyses, indirect costs, including those associated with productivity losses, were assumed to be captured in the QALY estimates [28].

Input parameters

Population characteristics and efficacy data for first-line regimens

A MEDLINE search and a review of scientific conference abstracts for clinical trials comparing the model's first-line regimens head-to-head identified four studies: Study 934 [15–17], Study CNA30024 [29], the ACTG 5202 study [18–19], and the ASSERT study [20–21]. None of these studies included all three first-line regimens. Study 934 and Study CNA30024 had comparable virologic efficacy endpoints (time to regimen failure) for all three first-line regimens, allowing for an indirect comparison of TDF/FTC and ABC/3TC. The ACTG 5202 study was excluded because full results with comparable endpoints have not been published; the ASSERT study was excluded because the unusually high drop-out rate confounded the efficacy results.

Characteristics of the modeled population, including baseline gender (86.5% male), mean age (38 years), and CD4⁺ cell-count distribution (Appendix S1 found at doi:10.1016/j.jval.2011.01.009), were assumed to be equivalent to those of the modified intent-to-treat population in Study 934, a head-to-head clinical trial comparing TDF/FTC and ZDV/3TC each in combination with EFV in treatment-naïve HIV-1–infected individuals [15–17]. Baseline characteristics available from study CNA30024, which compared ABC with ZDV each used in combination with 3TC and EFV, were similar.

Clinical efficacy and safety data for the TDF/FTC plus EFV arm and the ZDV/3TC plus EFV arm of the model were derived from the 144-week results of Study 934 [15–17]. Efficacy and safety data for the ABC/3TC plus EFV arm of the model were estimated from the 48-week results of Study CNA30024 [29]. These two trials both included ZDV/3TC plus EFV, which allowed for a direct comparison between TDF/FTC and ZDV/3TC and an indirect comparison between TDF/FTC and ABC/3TC. To make the indirect comparison, efficacy parameters (virologic response and CD4⁺ cell-count changes) for ABC/3TC were estimated by applying the relative difference between the ABC/3TC arm and the ZDV/3TC arm of Study CNA30024 to the

Table 1 – Clinical efficacy for individuals on first-line therapy.

Model input	TDF/FTC + EFV [15-17]	ZDV/3TC + EFV [15-17]	ABC/3TC + EFV [29]*
Virologic response (HIV-1 RNA < 400 copies/mL) through year 3			
24 weeks	89.8%	79.8%	83.2%
48 weeks	84.4%	72.4%†	75.5%†
96 weeks	73.7%	61.9%	64.5%
144 weeks	70.9%	58.1%	60.5%
Modeled virologic response after year 3			
Annual probability of switching therapy line	0.0913	0.1135	0.1135
Immunologic response			
Mean (SD) $CD4^+$ cell-count increase from baseline to 48 weeks (cells/μL)	190 (111.7)	158‡ (107.3)	213‡ (144.7)
Mean (SD) $CD4^+$ cell-count increase from baseline to 96 weeks (cells/μL)	270 (147.5)	237 (136.4)	320 (183.9)
Mean (SD) $CD4^+$ cell-count increase from baseline to 144 weeks (cells/μL)	312 (161.2)	271 (147.4)	365 (198.8)
Long-term (after year 3) mean annual $CD4^+$ cell-count increase (cells/μL)	21	17	22.9

3TC, lamivudine; ABC, abacavir; EFV, efavirenz; FTC, emtricitabine; HIV-1, human immunodeficiency virus; RNA, ribonucleic acid; SD, standard deviation; TDF, tenofovir DF; ZDV, zidovudine.

* All efficacy data for ABC/3TC + EFV were estimated by multiplying the Study 934 data for ZDV/3TC + EFV by the relative difference between the ABC/3TC + EFV and the ZDV/3TC + EFV arms of Study CNA30024.

† Virologic response at 48 weeks in Study CNA30024: ZDV/3TC + EFV = 71%; ABC/3TC + EFV = 74% [29].

‡ Median $CD4^+$ cell-count increases at 48 weeks in Study CNA30024: ZDV/3TC + EFV = 155 cells/μL; ABC/3TC + EFV = 209 cells/μL [29].

ZDV/3TC arm of Study 934. This technique maintained the same relative difference between ABC/3TC and ZDV/3TC in the model as was observed in Study CNA30024, allowing for a balanced comparison between the three first-line HAART regimens.

The proportion of clinical trial participants remaining on first-line therapy with HIV-1 RNA less than 400 copies/mL at various time points was used to determine the proportion of individuals remaining on first-line therapy during each of the first 3 years of the model. Beyond year 3, the model extrapolated data from baseline through week 144, using an exponential function to estimate an annual probability of switching from first line (Table 1).

Immunologic response, measured by annual increase in $CD4^+$ cell count, was used to estimate the transition probabilities between the $CD4^+$ cell-count health states of the model. Specifically, transition probabilities were calculated from the means and standard deviations of the $CD4^+$ cell-count increases observed at 48, 96, and 144 weeks in Study 934 and from the mean increase observed at 48 weeks in Study CNA30024. After week 144 (year 3), the model allowed for a modest continued increase in $CD4^+$ cell count for those individuals still on first-line therapy (Table 1) (Appendix S2 found at doi:10.1016/j.jval.2011.01.009).

Efficacy data for post–first-line regimens

In subsequent therapy lines, individuals received treatment according to US treatment guidelines [9] and current clinical practice. Individuals received a PI-based regimen as second-line therapy and raltegravir, etravirine, darunavir/r, and two NRTIs as third-line therapy. For non-suppressive therapy, the model assumed individuals would remain on a drug regimen equal in cost to their third-line regimen, despite the initiation of treatment failure. While on each post–first-line regimen in the model, individuals experienced an average annual change in $CD4^+$ cell count based on studies of HIV-infected individuals at different stages of disease (Table 2) [30–33].

Table 2 – Summary of regimens used, cost, and clinical efficacy for HIV-1–infected individuals receiving HAART, by therapy line.

	Second line	Third line	Non-suppressive
HAART regimen [9]	Lopinavir/r (40%) or atazanavir/r (60%) + 2 NRTIs*	Raltegravir + etravirine + darunavir/r + 2 NRTIs*	Raltegravir + etravirine + darunavir/r + 2 NRTIs*
Annual cost (2009 USD) [9,34]	$21,933	$46,034	$46,034
Median time on therapy (years) [27]	4.3	4.2	N/A
Annual probability of switching	0.149	0.152	0.000
Annual change in $CD4^+$ cell count [30–33]	+46.90 cells/μL	+41.00 cells/μL†	–22.00 cells/μL

HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus; N/A, not applicable; NRTI, nucleotide/nucleoside reverse transcriptase inhibitor; /r, boosted with low-dose ritonavir; USD, US dollars.

* NRTIs used in each therapy line are assumed to be in the following mix: 60% tenofovir DF/emtricitabine, 20% zidovudine/lamivudine, and 20% abacavir/lamivudine.

† For third-line therapy, the average was estimated using the $CD4^+$ cell-count increase from baseline to 48 weeks (108 cells) and assuming the $CD4^+$ cell-count increase observed between 24 and 48 weeks (9 cells), continued for the remaining time on therapy [31–32]. The total increase then was divided by the median time on therapy [27].

Table 3 – Annual non-ARV medical and medication costs, utility values, and AIDS-related mortality, by CD4⁺ cell-count range.

CD4⁺ cell-count range	Medical costs (2009 USD) [35]*	Non-ARV drug costs (2009 USD) [35]*	Utility values [38]	Annual probability of AIDS-related death [1]†
0–50	$41,469	$9957	0.778	0.162
51–100	$19,505	$6540	0.841	0.054
101–200	$19,505	$6540	0.841	0.022
201–350	$14,037	$4173	0.841	0.008
351–500	$14,037	$4173	0.937	0.004
> 500	$9473	$3397	0.937	0.004

AIDS, acquired immune deficiency syndrome; ARV, antiretroviral; USD, US dollars.
* Costs were inflated to 2009 USD using the medical care component of the US consumer price index [37].
† Annual rates were converted to annual probabilities using the equation $1 - e^{-\text{rate}}$.

In each year of the model, a certain percentage of individuals in each therapy line switched to the next therapy line. The annual probabilities of switching were calculated from the median time on each therapy line as observed in a recent United Kingdom cohort study by Beck and colleagues [27]. Individuals on non-suppressive therapy were assumed to remain on non-suppressive therapy until death (Table 2).

Cost data

First-line annual antiretroviral drug costs for TDF/FTC, ABC/3TC, and ZDV/3TC, each in combination with EFV, were $16,819, $16,391, and $15,621, respectively. For each subsequent therapy line, average annual antiretroviral drug costs were estimated based on the HAART regimens used (Table 2). Drug costs were taken from the wholesale acquisition cost from the Red Book [34] for the indicated daily dose for each antiretroviral drug.

Individuals in each CD4⁺ cell-count range in the model incurred costs while in that health state. Annual non-antiretroviral medical and medication costs by CD4⁺ cell-count range were derived from a US study by Gebo and colleagues [35], which estimated inpatient, outpatient, and emergency department utilization and costs through interviews with HIV-infected participants (Table 3).

Lastly, resource use (additional laboratory tests, a resistance assay, and a clinician visit) for switching therapy line was based on clinical expert opinion, and the cost ($829 per switch) [36] was assumed the same for each switch.

All costs were inflated to 2009 US dollars, when necessary, using the medical care component of the consumer price index [37].

Utility and mortality data

In each CD4⁺ cell-count range, individuals were assumed to experience different levels of quality of life, quantified by different utility weights. Utility weights taken from community-based preferences [38] were mapped to the model health states as follows: AIDS (CD4⁺ range 0–50), symptomatic HIV-1 infection (CD4⁺ range 50–350), and asymptomatic HIV-1 infection (CD4⁺ range > 350) (Table 3).

Mortality was modeled using an annual probability of death due to causes related or unrelated to AIDS. For AIDS-related causes, the model used mortality rates by CD4⁺ cell-count range [1] and converted these rates to probabilities (Table 3). The probability of death from non–AIDS-related causes was based, in part, on age- and gender-specific 2006 US general population mortality data [39], weighted by the percentage of males and females in the modeled population. Individuals entered the model at age 38; an annual adjustment factor, estimated by fitting an exponential curve to age-specific mortality data, was applied to account for aging. A relative risk value of 2.5 [40] was applied to the general population mortality data, to account for higher non–AIDS-related mortality rates observed among individuals with HIV-1 than in the general population. This relative-risk value does not include AIDS-related deaths but captures other causes of elevated death rates among individuals with HIV, such as drug overdose, hepatitis co-infection, or cardiovascular disease [4–5], which is now known to be associated with HIV-1 itself and some antiretroviral therapies.

Adverse events

Adverse events (anemia, lipoatrophy, myocardial infarction) that impact significantly different proportions of individuals between arms of the model were modeled explicitly to capture the (differential) effects on costs, quality of life, and adherence. In addition, the model included the one-time cost for the HLA-B*5701 screening test for individuals in the ABC/3TC arm of the model and annual renal monitoring costs for individuals in the TDF/FTC arm of the model [41-45] (Table 4).

Model outcomes

The model estimated total direct medical costs, including antiretroviral drugs costs, costs for adverse events, other medical costs (including costs for disease monitoring, switching therapy lines, treating opportunistic and other infections and adverse events other than those explicitly modeled), and non-antiretroviral drug costs. Health outcomes included life-years, QALYs, years on first-line therapy, percentages of deaths due to AIDS-related causes, and percentages of people remaining on first-line therapy (for time horizons shorter than remaining lifetime only). Incremental cost-effectiveness ratios included the incremental cost per life-year gained and per QALY gained. As recommended for US cost-effectiveness analyses, all costs and outcomes were discounted at a 3% annual rate [28].

Uncertainty and variability analyses

In addition to the base-case analysis, extensive analyses were performed to evaluate the impact of parameter uncertainty on the model results. One-way sensitivity analysis was performed using realistic ranges for each parameter derived from published sources to the extent possible (Appendix S1). Probabilistic sensitivity analysis was performed by simultaneously sampling all input parameters from appropriate probability distributions in 10,000 Monte Carlo simulations (Appendix S1). In addition, variability analysis was conducted to test the impact of modeling assumptions, including the model time horizon, discount rate, and incidence and cost of adverse events.

Table 4 – Incidence, costs, and utility decrements for adverse events during first-line therapy.

Adverse event	TDF/FTC + EFV	ABC/3TC + EFV	ZDV/3TC + EFV
Anemia			
Incidence in year 1 [15,29]	0.39%	2.16%	5.12%*
One-time treatment cost [41]	$5349	$5349	$5349
Lipoatrophy			
Two-year incidence [24]	11.94%	11.94%†	39.68%
Annual utility decrement during first line [42]	0.10	0.10	0.10
Myocardial infarction			
Annual incidence during first line [43]	0.37%	0.54%	0.32%
Treatment cost in first year [44]	$16,978	$16,978	$16,978
Treatment cost in subsequent years [44]	$3608	$3608	$3608
Annual utility decrement during remaining lifetime [45]	0.12	0.12	0.12
HLA-B*5701 one-time screening cost [36]	$0	$88	$0
Annual cost for renal monitoring during first-line therapy [36]	$69	$0	$0

3TC, lamivudine; ABC, abacavir; EFV, efavirenz; FTC, emtricitabine; TDF, tenofovir DF; ZDV, zidovudine.
* Percentage of individuals developing anemia at 48 weeks in the ZDV/3TC + EFV arm of Study CNA30024 = 5.23% [29].
† Incidence of lipoatrophy for ABC/3TC was assumed equal to that observed in the tenofovir arm of the ACTG 5142 metabolic substudy [24].

Results

Base-case results

The model estimated that TDF/FTC had the lowest discounted lifetime costs ($747,327) compared with either ABC/3TC ($777,090) or ZDV/3TC ($778,287) (Table 5). Antiretroviral drugs represented approximately 65% of lifetime costs for all arms. The model estimated that TDF/FTC resulted in more life-years and QALYs compared with either ABC/3TC or ZDV/3TC. Therefore, TDF/FTC was the dominant first-line treatment option, exhibiting lower costs and more QALYs compared with both ABC/3TC and ZDV/3TC.

Uncertainty analysis results

One-way sensitivity analysis demonstrated that the model results were most sensitive to efficacy parameters for the first-line regimens (virologic response, $CD4^+$ cell-count increases), annual change in $CD4^+$ cell count in later therapy lines, and antiretroviral drug costs in later therapy lines. For the pair-wise comparison between TDF/FTC and ZDV/3TC, TDF/FTC remained the dominant treatment strategy (i.e., exhibited lower costs and better health outcomes) for all ranges tested in the one-way sensitivity analysis. TDF/FTC remained dominant compared with ABC/3TC for all ranges tested, with the exception of instances in which the sensitivity analysis examined $CD4^+$ cell-count increases that were higher for ABC/3TC than for TDF/FTC. In these cases, ABC/3TC exhibited higher costs and more QALYs than TDF/FTC, but the incremental cost-effectiveness ratio of ABC/3TC versus TDF/FTC remained above $96,000 per QALY gained.

Probabilistic sensitivity analysis revealed that TDF/FTC was cost-effective compared with ABC/3TC and ZDV/3TC in more than 75% of all simulation runs for every willingness-to-pay threshold between $0 and $250,000 per QALY gained (Fig. 2). Specifically, at a willingness to pay of $50,000 per QALY gained, TDF/FTC was predicted to be cost-effective 88.1% of the time, compared with 7.8% for ABC/3TC and 4.1% for ZDV/3TC.

Variability analysis results

Short-term model results found that, compared with the other two first-line regimens, a larger percentage of individuals remained on TDF/FTC at 5 years (19%–23% more). Undiscounted lifetime results revealed that individuals initiating therapy with TDF/FTC remained on first-line therapy 2.4 and 2.7 years longer than individuals initiating therapy with ABC/3TC or ZDV/3TC, respectively. The incremental results of the model were consistent for different time horizons and discount rates, with TDF/FTC being the dominant first-line treatment strategy in most cases. Conclusions of the model also did not change when myocardial infarction rates were set equal to zero for all arms (Table 5). Additional scenarios testing a rate of 5% for hypersensitivity reaction instead of HLA-B*5701 screening for the ABC/3TC arm or a rate of 2% for renal toxicity for the TDF/FTC arm showed that TDF/FTC remained the dominant treatment strategy (results not shown).

Discussion

This analysis demonstrates that initiating HAART with TDF/FTC plus EFV (the components of Atripla) resulted in lower lifetime costs and more years on first-line therapy, life-years, and QALYs, compared with either ABC/3TC plus EFV or ZDV/3TC plus EFV as a first-line regimen in treatment-naïve adults with HIV-1 infection. Model results were driven by better virologic response in the TDF/FTC arm, which allowed more individuals to delay higher-cost, later-line therapy and eventual disease progression.

In general, sensitivity analysis found that the results of the model were robust. Probabilistic sensitivity analysis showed that TDF/FTC was cost-effective, compared with ABC/3TC and ZDV/3TC, the large majority of the time (> 75%) over a wide range of willingness-to-pay thresholds. The model was sensitive to the clinical data (particularly for the comparison between TDF/FTC and ABC/3TC), indicating the importance of including head-to-head data for these two regimens. Nevertheless, the cost-effectiveness results supported the US clinical treatment guidelines, which recommend TDF/FTC as the preferred NRTI pair for treatment-naïve individuals [9].

To our knowledge, there is only one other US study comparing NNRTI-based regimens in treatment-naïve individuals: Schackman and colleagues [46] found that initiating HAART with ABC/3TC and the HLA-B*5701 screening test was cost-effective if ABC/3TC had efficacy equal to TDF/FTC. Our study, which attempted to model the difference in efficacy between ABC/3TC and TDF/FTC via an indirect comparison using data from two head-to-head clinical trials, found that TDF/FTC dominated ABC/3TC in the base-case analysis. However, the results of both our model and the Schackman model are sensitive to assumptions about efficacy,

Table 5 – Costs, outcomes, and cost-effectiveness of TDF/FTC + EFV compared with ABC/3TC + EFV and ZDV/3TC + EFV.

Scenario	TDF/FTC + EFV	ABC/3TC + EFV	ZDV/3TC + EFV
Base case (discounted lifetime results)*			
Costs			
Antiretroviral drug costs	$482,657	$512,343	$508,948
Adverse-event costs†	$2305	$2320	$1480
Other medical costs‡	$196,911	$197,057	$201,630
Other medication costs	$65,453	$65,370	$66,229
Total costs	$747,327	$777,090	$778,287
Heath outcomes			
Life years	17.22	17.14	17.06
QALYs	15.75	15.68	15.44
Years on first-line therapy	7.70	6.05	5.84
Incremental cost per life year gained		–$363,683§	–$187,252§
Incremental cost per QALY gained		–$440,368§	–$100,860§
Results at 5-year time horizon*			
Total costs	$161,963	$163,515	$164,540
QALYs	4.116	4.117	4.032
Incremental cost per QALY gained		$1,080,351§	–$30,598§
Percentage remaining on first-line therapy at 5 years	55.6%	44.8%	43.0%
Undiscounted lifetime results			
Total costs	$1,200,257	$1,249,208	$1,247,550
Life years	26.23	26.06	25.88
QALYs	24.00	23.83	23.48
Incremental cost per QALY gained		–$295,835§	–$91,827§
Years on first-line therapy	9.83	7.37	7.11
Percentage of deaths due to AIDS-related causes	20.6%	21.9%	22.9%
Excluding myocardial infarction*			
Total costs	$745,575	$774,974	$777,081
QALYs	15.80	15.74	15.48
Incremental cost per QALY gained		–$511,665§	–$98,211§

3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; EFV, efavirenz; FTC, emtricitabine; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TDF, tenofovir DF; ZDV, zidovudine.

* All costs and outcomes discounted at 3% per year.

† Includes costs for anemia, myocardial infarction, HLA-B*5701 screening, and renal monitoring.

‡ Includes costs for disease monitoring, switching therapy lines, treatment of opportunistic and other infections, and adverse events other than anemia, myocardial infarction, HLA-B*5701 screening, and renal monitoring.

§ Negative ICER indicates that TDF/FTC + EFV costs less and results in better health outcomes than the comparator.

emphasizing again the importance of utilizing head-to-head data when available.

For any model, it is important to compare clinically relevant outcomes of the model with observational studies, to validate how well the model matches real-world data. Cohort studies have reported increases in life expectancy over time and have found that life expectancy varies widely, depending on the year in which HAART was initiated, age, gender, history of injection drug use, and baseline viral load and CD4$^+$ cell count [4,6,47–48]. A recent study following HIV-infected individuals estimated that life expectancy for a person aged 35 years has increased from 25.0 years for individuals initiating therapy from 1996 to 1999, to 37.3 years for those initiating therapy from 2003 to 2005 [6]. The lower life expectancy predicted by our model (26 years) reflects the modeled population (based on participants in Study 934), nearly half of which had a baseline CD4$^+$ cell count less than 200 cells/μL, and our somewhat conservative assumptions about the duration of first-line therapy. Notably, our results for estimated life expectancy are within the range (19.2–34.2 years) estimated by other economic models [8,49,50]. Our model also predicted that for HIV-infected individuals initiating HAART in the US today (i.e., in 2011), approximately 21% would die of AIDS-related causes. As expected, this result is lower than the percentages found in US observational studies (25%–56%) [2–5] because our model included new, highly efficacious drugs. These results corroborate recent evidence that as new HIV-1 treatment regimens are introduced, the risk of death from AIDS-related causes may continue to decrease and life expectancy may continue to increase.

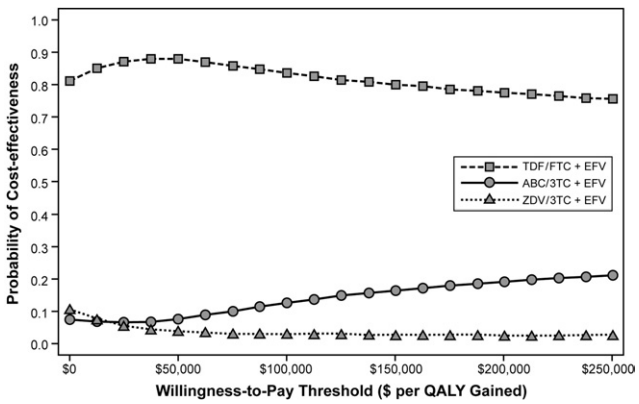

Fig. 2 – Cost-effectiveness acceptability curves. 3TC, lamivudine; ABC, abacavir; EFV, efavirenz; FTC, emtricitabine; QALY, quality-adjusted life year; TDF, tenofovir DF; ZDV, zidovudine.

One of the strong points of our model is that the comparison of TDF/FTC and ZDV/3TC is based on head-to-head clinical trial data

collected over a follow-up period of nearly 3 years. The availability of 144-week data improves the reliability of long-term efficacy estimates extrapolated for these two HAART regimens after 144 weeks. In addition, we explicitly modeled adverse events that were significantly different between the three first-line comparator regimens. Interestingly, our model showed that the cost of treating adverse events for all three regimens was relatively small compared with lifetime costs (< 1%). Thus, while safety profiles of HAART regimens are clinically important, adverse events had a limited impact on the model's economic outcomes, mostly due to relatively low treatment costs compared with antiretroviral drug costs.

Our analysis has several limitations that should be well understood in interpreting the results. First, the results of this analysis are restricted to first-line, EFV-based HAART regimens with brand pricing and full regimen switches upon therapy failure. The analysis did not consider other NNRTIs (e.g., nevirapine for pregnant women), third agents from other drug classes, generic drug pricing, or drug substitutions within regimens. This approach was chosen as a first iteration of the model in order to help inform clinicians about the cost-effectiveness of first-line, EFV-based regimens. A more complex analysis would be necessary to model and to evaluate the cost-effectiveness of all possible first-line therapy options.

Also, recent results of the ACTG 5202 trial reported that TDF/FTC was significantly more efficacious compared with ABC/3TC among individuals with high baseline viral loads (≥ 100,000 copies/mL) but not among individuals with low baseline viral loads. Therefore, the results of our analysis, which included better virologic efficacy for TDF/FTC overall, may be most applicable to individuals who initiate therapy with high viral loads [18–19].

Finally, an indirect comparison between TDF/FTC and ABC/3TC was necessary in the absence of head-to-head clinical trial data. However, Study 934 and Study CNA30024 reported remarkably similar results for ZDV/3TC in combination with EFV. Thus, efficacy data for ABC/3TC from Study CNA30024 required only a small (upward) adjustment, which was conservative relative to TDF/FTC. Clinical trials comparing TDF/FTC and ABC/3TC, both with EFV, in treatment-naïve individuals are currently ongoing [18–21]. Results from the ACTG 5202 trial showed that, among the subgroup of participants receiving EFV, more participants receiving TDF/FTC (89.8%) than ABC/3TC (85.3%) remained free of virologic failure at 96 weeks [19]. Once full results of the ACTG 5202 trial are published (specifically time to regimen failure), our model's comparison of TDF/FTC with ABC/3TC will be more reliable.

This study revealed that among those initiating HAART with EFV-based regimens, individuals using TDF/FTC may have lower costs and better short- and long-term health outcomes, compared with individuals using either ABC/3TC or ZDV/3TC. More individuals with durable viral suppression yielded better clinical outcomes and cost savings, due to the postponement of more expensive subsequent lines of therapy and lower costs associated with disease-related resource use.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi10.1016/j.jval.2011.01.009, or if hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 2003;362:22–9.
[2] Crum NF, Riffenburgh RH, Wegner S, et al. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. J Acquir Immune Defic Syndr 2006;41:194–200.
[3] Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43:27–34.
[4] Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. Ann Intern Med 2007;146:87–95.
[5] Krentz HB, Kliewer G, Gill MJ. Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. HIV Med 2005;6:99–106.
[6] Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372:293–9.
[7] Holtgrave DR, Pinkerton SD. Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. J Acquir Immune Defic Syndr Hum Retrovirol 1997;16:54–62.
[8] Schackman BR, Gebo KA, Walensky RP, et al. The lifetime cost of current human immunodeficiency virus care in the United States. Med Care 2006;44:990–7.
[9] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services; December 1, 2009. Available from: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf. [Accessed December 29, 2009].
[10] Gifford AL, Bormann JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. J Acquir Immune Defic Syndr 2000;23:386–95.
[11] Jordan J, Tolson J, Delea T, et al. Impact of fixed-dose combination zidovudine/lamivudine on adherence to antiretroviral therapy: a retrospective claims-based cohort study [Poster]. Presented at: 6th International Congress on Drug Therapy in HIV Infection. Glasgow, UK, November 17–21, 2002.
[12] Portsmouth SD, Osorio J, McCormick K, et al. Better maintained adherence on switching from twice-daily to once-daily therapy for HIV: a 24-week randomized trial of treatment simplification using stavudine prolonged-release capsules. HIV Med 2005;6:185–90.
[13] Antiretroviral Therapy Cohort Collaboration. Rates of disease progression according to initial highly active antiretroviral therapy regimen: a collaborative analysis of 12 prospective cohort studies. J Infect Dis 2006;194:612–22.
[14] Bartlett JA, Chen SS, Quinn JB. Comparative efficacy of nucleoside/nucleotide reverse transcriptase inhibitors in combination with efavirenz: results of a systematic overview. HIV Clin Trials 2007;8:221–6.
[15] Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med 2006;354:251–60.
[16] Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes – a 96-week analysis. J Acquir Immune Defic Syndr 2006;43:535–40.
[17] Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. J Acquir Immune Defic Syndr 2008;47:74–8.

[18] Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. N Engl J Med 2009; 361:2230–40.
[19] Daar E, Tierney C, Fischl M, et al. ACTG 5202: final results of ABC/3TC or TDF/FTC with either EFV or ATV/r in treatment-naïve HIV-infected patients [Podium Presentation]. Presented at: 17th Conference on Retroviruses & Opportunistic Infections. San Francisco, CA, February 16-19, 2010.
[20] Stellbrink HJ, Moyle G, Orkin C, et al. Assessment of safety and efficacy of abacavir/lamivudine and tenofovir/emtricitabine in treatment-naïve HIV-1 infected subjects. ASSERT: 48-week results [Abstract]. Presented at: 12th European AIDS Conference. Cologne, Germany, November 11-14, 2009.
[21] Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. J Acquir Immune Defic Syndr 2010;55:49–57.
[22] Hill A, Sawyer W. Effects of nucleoside reverse transcriptase inhibitor backbone on the efficacy of first-line boosted highly active antiretroviral therapy based on protease inhibitors: meta-regression analysis of 12 clinical trials in 5168 patients. HIV Med 2009;10:527–35.
[23] Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2008;358:2095–106.
[24] Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. AIDS 2009;23:1109–18.
[25] Young J, Bucher HC, Guenthard HF, et al. Virologic and immunologic responses to efavirenz or boosted lopinavir as first therapy for patients with HIV in the Swiss HIV Cohort Study [Poster]. Presented at: 5th International AIDS Society Conference on HIV Pathogenesis and Treatment. Cape Town, South Africa, July 19-22, 2009.
[26] Sierra-Madero J, Villasis-Keever A, Méndez P, et al. Prospective, randomized, open label trial of efavirenz vs lopinavir/ritonavir in HIV+ treatment-naive subjects with CD4+<200 cell/mm^3 in Mexico. J Acquir Immune Defic Syndr 2010;53:582–8.
[27] Beck EJ, Mandalia S, Youle M, et al. Treatment outcome and cost-effectiveness of different highly active antiretroviral therapy regimens in the UK (1996–2002). Int J STD AIDS 2008;19:297–304.
[28] Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. New York: Oxford University Press, 1996.
[29] DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. Clin Infect Dis 2004;39: 1038–46.
[30] Phillips AN, Ledergerber B, Bogner JR, et al. Rate of change in CD4 counts in patients with stable HIV viremia [Poster]. Presented at: 9th International Congress on Drug Therapy in HIV Infection. Glasgow, UK, November 9-13, 2008.
[31] Yazdanpanah Y, Fagard C, Descamps D, et al. High rate of virologic success with raltegravir plus etravirine and darunavir/ritonavir in treatment-experienced patients with multidrug-resistant virus: results of the ANRS 139 TRIO trial [Podium Presentation]. Presented at: 17th International AIDS Conference. Mexico City, Mexico, August 3–8, 2008.
[32] Fagard C, Descamps D, Dubar V, et al. Efficacy and safety of raltegravir plus etravirine and darunavir/ritonavir in treatment-experienced patients with multidrug-resistant virus: 48-week results from the ANRS 139 TRIO trial [Abstract]. Presented at: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention. Cape Town, South Africa, July 19–22, 2009.
[33] Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet 2004;364:51–62.
[34] Red Book for Windows. Version 61127. Volume 53. Montvale, NJ: Thomson PDR, 2009.
[35] Gebo K, Fleishman J, Conviser R, et al. Contemporary costs of HIV health care in the HAART era [Poster]. Presented at: 13th Conference on Retroviruses and Opportunistic Infections. Denver, CO, February 5–8, 2006.
[36] The Essential RBRVS 2009. A Comprehensive Listing of RBRVS Values for CPT and HCPCS Codes. Salt Lake City, Utah: Ingenix, Inc., 2009.
[37] Bureau of Labor Statistics. Medical care component of consumer price index—all urban consumers (current series), not seasonally adjusted. US Department of Labor; June 2009. Available from: http://www.bls.gov/CPI/. [Accessed August 31, 2009].
[38] Schackman BR, Goldie SJ, Freedberg KA, et al. Comparison of health state utilities using community and patient preference weights derived from a survey of patients with HIV/AIDS. Med Decis Making 2002;22:27–38.
[39] Heron M, Hoyert DL, Murphy SL, et al. Deaths: final data for 2006. Natl Vital Stat Rep 2009;57:1–134.
[40] Lewden C, Chene G, Morlat P, et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm^3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. J Acquir Immune Defic Syndr 2007;46:72–7.
[41] Curkendall SM, Doan QV, Everhard F, et al. Direct costs of anemia among patients treated with zidovudine [Poster]. Presented at: 12th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research. Arlington, VA, May 19–23, 2007.
[42] Lenert LA, Feddersen M, Sturley A, Lee D. Adverse effects of medications and trade-offs between length of life and quality of life in human immunodeficiency virus infection. Am J Med 2002;113:229–32.
[43] Lundgren J, Reiss P, Worm S, et al. Risk of myocardial infarction with exposure to specific ARV from the PI, NNRTI, and NRTI drug classes: the D:A:D study [Abstract]. Presented at: 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada, February 8-11, 2009.
[44] Pignone M, Earnshaw S, Pletcher MJ, Tice JA. Aspirin for the primary prevention of cardiovascular disease in women: a cost-utility analysis. Arch Intern Med 2007;167:290–5.
[45] Tsevat J, Goldman L, Soukup JR, et al. Stability of time-tradeoff utilities in survivors of myocardial infarction. Med Decis Making 1993;13:161–5.
[46] Schackman BR, Scott CA, Walensky RP, et al. The cost-effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. AIDS 2008;22:2025–33.
[47] Lima VD, Hogg RS, Harrigan PR, et al. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. AIDS 2007;21:685–92.
[48] Lloyd-Smith E, Brodkin E, Wood E, et al. Impact of HAART and injection drug use on life expectancy of two HIV-positive cohorts in British Columbia. AIDS 2006;20:445–50.
[49] Munakata J, Benner JS, Becker S, et al. Clinical and economic outcomes of nonadherence to highly active antiretroviral therapy in patients with human immunodeficiency virus. Med Care 2006;44:893–9.
[50] Braithwaite RS, Justice AC, Chang CC, et al. Estimating the proportion of patients infected with HIV who will die of comorbid diseases. Am J Med 2005;118:890–8.